PATENT SPECIFICATION

627,139

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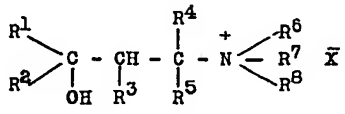
PROVISIONAL SPECIFICATION

Improvements in and relating to the Preparation of Quaternary Ammonium Salts of Substituted Propanolamines, Allylamines and Propylamines

We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, a British Company, and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention to be as follows:—

This invention relates to a process for the preparation of new derivatives of substituted γ-hydroxypropylamines, substituted allylamines and substituted propylamines, and has for its object the preparation of certain novel and useful compounds, namely quaternary ammonium salts derived from γγ-disubstituted-γ-hydroxypropylamines, γγ-disubstituted-allylamines and γγ-disubstituted propylamines. No claim is made herein to the aforesaid compounds from which the novel quaternary ammonium salts to which our invention relates are derived.

According to our invention we prepare N - trisubstituted - γγ - disubstituted - γ-hydroxypropylammonium salts, N-trisubstituted - γγ - disubstituted - allylammonium salts and N-trisubstituted-γγ-disubstituted-propylammonium salts of the general formula:—



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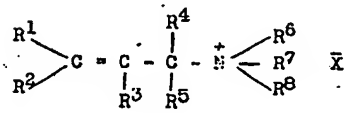

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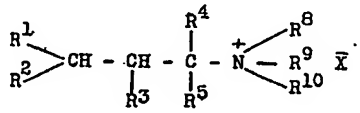


(III)

wherein R^1 and R^2 may be either identical or different and denote aryl, aralkyl or *cyclo*alkyl radicals, optionally substituted, for example, by alkyl or alkoxy groups,

R^3 denotes hydrogen or an alkyl radical

R^4 denotes hydrogen or an alkyl radical

R^5 denotes hydrogen or an alkyl, aryl or aralkyl radical

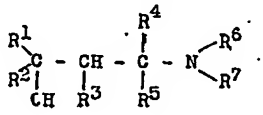
R^6 and R^7 may be either identical or different and denote alkyl, alkenyl, *cyclo*-alkyl, aryl or aralkyl groups, or —NR^6R^7 may denote the pyrrolidino-, morpholino- or piperidino-group, optionally substituted by one or more alkyl groups,

R^8 denotes an alkyl or aralkyl radical,

R^9 and R^{10} may be either identical or different and denote alkyl, *cyclo*alkyl, aryl or aralkyl radicals, or—NR^9R^{10} may denote the pyrrolidino-, morpholino-, or piperidino-group, optionally substituted by one or more alkyl groups,

$\bar{X}$ is an acid radical such as chloride, bromide, iodide or methosulphate radical.

In accordance with our invention, these quaternary salts are made by treating an alkyl or aralkyl halide or other reactive acid salt R^8X with a tertiary amine of the general formula



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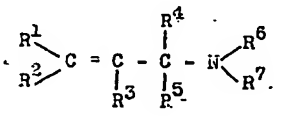

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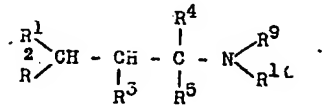


(VI)

(wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} have the same meaning as above) or *vice versa*.

The quaternisation, in accordance with our invention, may be effected in a solvent (such as anhydrous acetone, ethyl alcohol, dioxan) at room temperature or at the boiling point of the solvent or at intermediate temperatures. Preferably an excess of the quaternising agent is employed. The solvent and the quantity used is preferably so selected that the quaternary salt crystallises from the reaction mixture on cooling. In cases when this cannot conveniently be done, a liquid in which the quaternary salt is insoluble (such as ether) is added gradually to the reaction product until crystallisation commences.

The N-disubstituted-$\gamma\gamma$-disubstituted-γ-hydroxypropylamines of general formula (IV) (above) may be prepared by bringing about a Grignard reaction between the appropriate β-tertiaryaminopropionic acid alkyl ester and an appropriate organo-magnesium halide and subsequently hydrolysing the organomagnesium compound so produced, or alternatively they may be made by bringing about a Grignard reaction between the appropriate β-tertiaryaminoethyl aryl ketone and an appropriate organomagnesium halide, and subsequently hydrolysing the organomagnesium compound so produced. The N-disubstituted-$\gamma\gamma$-disubstituted-allylamines of general formula (V) (above) are prepared by removal of the elements of water from the corresponding γ-hydroxy-propylamines of general formula (IIV (above). The N-disubstituted-$\gamma\gamma$-disubstituted-propylamines of general formula (VI) (above) are prepared by reduction of the corresponding allylamines of general formula (V) (above).

The new quaternary salts to which this invention relates are crystalline compounds, soluble in water. They are useful as therapeutic agents.

The following examples illustrate the invention:

EXAMPLE 1.

A solution of the ethyl ester of β-piperidinopropionic acid (37 parts by weight) in dry ether is added gradually to an ether solution of the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts), stirred and cooled in a bath kept at 0° C. After stirring in the cold for 1 hour, the reaction mixture is heated under reflux for 2 hours and is then cooled to 0° C. and stirred into crushed ice. Concentrated hydrochloric acid is then gradually added to the stirred mixture which is cooled to 0° C., until acid to congo red. After standing for 1 hour at 0°C., the salt which separates is filtered off and washed with ether. The salt is suspended in chloroform and the suspension shaken with excess of concentrated ammonia solution and the chloroform layer separated, washed with water and dried. The chloroform is evaporated, leaving 1:1-diphenyl-3-piperidinopropanol as a solid residue, which after recrystallisation from benzene or light petroleum, forms crystals which melt at 120—121° C. (uncorrected).

1:1-Diphenyl-3-piperidinopropanol (1 part) is dissolved in anhydrous acetone (10 parts), methyl iodide (1 part) added and the mixture boiled under reflux for 15 minutes. On cooling N-methyl-3-hydroxy - 3:3 - diphenylpropylpiperidinium iodide crystallises out and after recrystallisation from alcohol has melting point 214—215° C. (uncorrected).

EXAMPLE 2.

1:1-Diphenyl - 3 - dimethylaminopropanol is prepared from the ethyl ester of β - dimethylaminopropionic acid (29 parts) and the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts) by a method essentially similar to that described in Example 1 (above) for the preparation of 1:1-diphenyl-3-piperidinopropanol. 1:1 - Diphenyl - 3 - dimethylaminopropanol has melting point 167° C. (uncorrected) after recrystallisation from benzene or light petroleum.

1:1-Diphenyl - 3 - dimethylaminopropanol (4 parts) is dissolved in boiling ethyl alcohol (80 parts) and ethyl iodide (5 parts) added and the mixture boiled under reflux for 2 hours. On cooling N-dimethyl-N-ethyl-3-hydroxy - 3:3 - diphenylpropylammonium iodide crystallises out and melts at 200—201° C. with decomposition (uncorrected) after recrystallisation from ethyl alcohol.

EXAMPLE 3.

1:1-Diphenyl - 3 - dimethylaminopropanol (2 parts) is dissolved in boiling ethyl alcohol (40 parts) and benzyl chloride (3 parts) added, and the mixture boiled under reflux for 2 hours. The mixture is cooled, ether (50 parts) is gradually added, and the crystals of N-dimethyl-N-benzyl - 3 - hydroxy - 3:3 - diphenylpropylammonium chloride filtered off and recrystallised from ethyl alcohol; melting point 251° C. (uncorrected) with decomposition.

EXAMPLE 4.

1:1 - Diphenyl - 3 - diethylaminopropanol is prepared from the ethyl ester of β-diethylaminopropionic acid (35 parts) and the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts) by a method essentially similar to that described in Example 1 (above) for the preparation of 1:1-diphenyl-3-piperidinopropanol. 1:1-Diphenyl-3-diethylaminopropanol, purified by distillation under reduced pressure (boiling point 154° C/0.2 mm.) or by recrystallisation from light petroleum has melting point 53° C. (uncorrected).

1:1 - Diphenyl - 3 - diethylaminopropanol (1 part) is dissolved in anhydrous acetone (2 parts), methyl iodide (1 part) in anhydrous acetone (2 parts) added and the mixture allowed to stand for 2 hours. N - Methyl-N-diethyl-3-hydroxy-3:3-diphenylpropylammonium iodide, which crystallises out, is recrystallised from methyl alcohol and has melting point 198—199° C. (uncorrected).

EXAMPLE 5.

A solution of 1:1-diphenyl-3-piperidinopropanol (3 parts) (prepared as described in Example 1) in concentrated aqueous hydrochloric acid (6 parts) and glacial acetic acid (20 parts) is boiled under reflux for 30 minutes. The solution is then evaporated to dryness under reduced pressure and the residual solid is dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ethereal solution is dried, the ether evaporated and the residual oil distilled under reduced pressure, when the product, 1:1-diphenyl-3-piperidino-1:2-propene is collected as a colourless liquid, boiling point 138° C/0.1 mm. pressure.

1:1 - Diphenyl-3-piperidino-1:2-propene (1 part) is dissolved in anhydrous acetone (3 parts) and a solution of methyl iodide (1 part) in acetone (1 part) is added, when heat is developed. After standing for several hours, the crystals of N - methyl-3:3-diphenyl-allylpiperidinium iodide which separates are removed by filtration and recrystallised from ethyl alcohol, melting point 189—190° C. (uncorrected) with decomposition.

EXAMPLE 6.

1:1-Diphenyl-3-piperidino - 1:2 - propene is converted to the hydrochloride by passing dry hydrogen chloride into a chloroform solution until acid to congo red and adding ether until crystallisation commences. The hydrochloride is then removed by filtration and recrystallised from a mixture of chloroform and acetone, melting point 209—210° C. (uncorrected).

1:1-Diphenyl-3-piperidino - 1:2 - propene hydrochloride (1 part) in ethyl alcohol (10 parts) is shaken at room temperature with platinum oxide (0.02 parts) (prepared according to the directions given in Organic Syntheses, 1932, Collective Vol. I, p. 452) in an atmosphere of hydrogen. When the theoretical amount of hydrogen has been absorbed (after approximately 3 hours), the catalyst is removed by filtration and the alcohol is removed by evaporation under reduced pressure. The residue is recrystallised from a mixture of alcohol and acetone, when 1:1 - diphenyl-3-piperidinopropane hydrochloric is obtained as crystals; melting point 215—217° C. (uncorrected). The free base is obtained by suspending the hydrochloride in water, adding excess aqueous ammonia and extracting with ether. The ethereal extract, after drying and evaporation of ether, yields crystals of 1:1-diphenyl-3-piperidinopropane; melting point 39—40° C. (uncorrected).

1:1-Diphenyl-3-piperidinopropane (1 part) is dissolved in anhydrous acetone (2 parts) and methyl iodide (1 part) in anhydrous acetone (1 part) is added. After standing for 2 hours the crystals of N - methyl - 3:3 - diphenylpropylpiperidinium iodide are filtered off and recrystallised from ethyl alcohol; melting point 175—176° C. (uncorrected) with decomposition.

EXAMPLE 7.

1:1 - Diphenyl-3-diallylaminopropanol is prepared from the ethyl ester of β-diallylaminopropionic acid (39 parts) and the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts) by a method essentially similar to that described in Example 1 (above) for the preparation of 1:1-diphenyl-3-piperidinopropanol. 1:1 - Diphenyl-3-diallylaminopropanol has boiling point 157—159° C/0.4 mm. and melting point 25—27° C. (uncorrected) after recrystallisation from light petroleum (boiling point 40—60° C).

1:1 - Diphenyl - 3 - diallylaminopro-

panol (3 parts) is dissolved in anhydrous acetone (5 parts) and methyl iodide (2 parts) added to the solution. The fine needles of N - methyl - N - diallyl-3-hydroxy - 3:3 - diphenylpropylammonium iodide which quickly separate, are recrystallised from aqueous ethyl alcohol; melting point 196—197° C. with decomposition (uncorrected).

EXAMPLE 8.

1:1 - Diphenyl - 3 - diallylamino-1:2-propene is prepared from 1:1-diphenyl-3-diallylaminopropanol by dehydration by a method essentially similar to that described in Example 5 for the preparation of 1:1-diphenyl-3-piperidinol-:2-propene. 1:1-Diphenyl-3-diallylamino-1:2-propene is obtained as a colourless oil, boiling point 134° C/0.2 mm. by distillation under reduced pressure.

1:1 - Diphenyl - 3 - diallylamino-1:2-propene (2 parts) is dissolved in anhydrous acetone (3 parts), methyl iodide (2 parts) added and the mixture heated under reflux for 1 hour. After cooling and standing for 24 hours, the crystals of N - methyl-N-diallyl-3:3-diphenylallylammonium iodide are separated by filtration and recrystallised from ethyl alcohol; melting point 149—151° C. (uncorrected) with decomposition.

Dated this 28th day of May, 1947.

THE WELLCOME FOUNDATION LTD.,
A. N. FALDER,
Secretary.

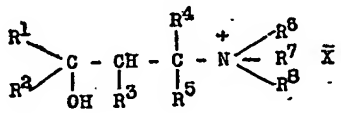
COMPLETE SPECIFICATION

Improvements in and relating to the Preparation of Quaternary Ammonium Salts of Substituted Propanolamines, Allylamines and Propylamines

We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, a British Company, and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to a process for the preparation of new derivatives of substituted γ-hydroxypropylamines, substituted allylamines and substituted propylamines, and has for its object the preparation of certain novel and useful compounds, namely quaternary ammonium salts derived from γγ-disubstituted-γ-hydroxypropylamines, γγ-disubstituted allylamines and γγ-disubstituted propylamines. No claim is made herein to the aforesaid compounds from which the novel quaternary ammonium salts to which our invention relates are derived.

According to our invention we prepare N - trisubstituted - γγ - disubstituted-γ-hydroxypropylammonium salts and N-trisubstitued - γγ - disubstituted-propylammonium salts of the general formula:—



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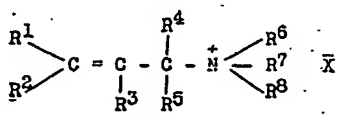

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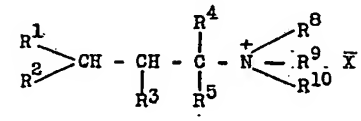


(III)

wherein R^1 and R^2 may be either identical or different and denote aryl, aralkyl or *cyclo*alkyl radicals, optionally substituted, for example, by alkyl or alkoxy groups,

R^3 denotes hydrogen or an alkyl radical

R^4 denotes hydrogen or an alkyl radical

R^5 denotes hydrogen or an alkyl, aryl or aralkyl radical

R^6 and R^7 may be either identical or different and denote alkyl, alkenyl, *cyclo*alkyl, aryl or aralkyl groups, or $—NR^6R^7$ may denote the pyrrolidino-, morpholino- or piperidino-group, optionally substituted by one or more alkyl groups,

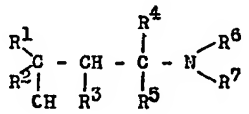
R^8 denotes an alkyl or aralkyl radical

R^9 and R^{10} may be either identical or different and denote alkyl, *cyclo*alkyl, aryl or aralkyl radicals, or $—NR^9R^{10}$

may denote the pyrrolidino-, morpholino-, or piperidino-group, optionally substituted by one or more alkyl groups, and

$\overline{X}$ is an acid radical such as chloride, bromide, iodide or methosulphate radical.

In accordance with our invention, these quaternary salts are made by treating an alkyl or aralkyl halide or other reactive acid salt R^8X with a tertiary amine of the general formula



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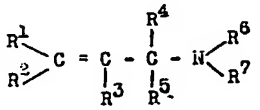

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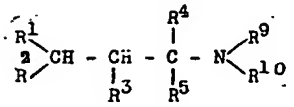
or



(VI)

(wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} have the same meaning as above) or *vice versa*.

The quaternisation, in accordance with our invention may be effected in a solvent (such as anhydrous acetone, ethyl alcohol, dioxan) at room temperature or at the boiling point of the solvent or at intermediate temperatures. Preferably an excess of the quaternising agent is employed. The solvent and the quantity used is preferably so selected that the quaternary salt crystallises from the reaction mixture on cooling. In cases when this cannot conveniently be done, a liquid in which the quaternary salt is insoluble (such as ether) is added gradually to the reaction product until crystallisation commences.

The N-disubstituted-$\gamma\gamma$-disubstituted-γ-hydroxypropylamines of general formula (IV) (above) may be prepared by bringing about a Grignard reaction between the appropriate β - tertiaryaminopropionic acid alkyl ester and an appropriate organo-magnesium halide and subsequently hydrolysing the organo-magnesium compound so produced, or alternatively they may be made by bringing about a Grignard reaction between the appropriate β-tertiaryaminoethyl aryl ketone and an appropriate organomagnesium halide, and subsequently hydrolysing the organiomagnesium compound so produced. The N-disubstituted-$\gamma\gamma$-disubstituted-allylamines of general formula (V) (above) are prepared by removal of the elements of water from the corresponding γ - hydroxy - propylamines of general formula (IV) (above). The N-disubstituted - $\gamma\gamma$ - disubstituted - propylamines of general formula (VI) (above) are prepared by reduction of the corresponding allylamines of general formula (V) (above).

The new quaternary salts to which this invention relates are crystalline compounds, soluble in water. They are useful as therapeutic agents having antispasmodic and broncho-dilating action.

The following examples illustrate the invention:—

EXAMPLE I.

A solution of the ethyl ester of β-piperidino-propionic acid (37 grams) in dry ether is added gradually to an ether solution of the Grignard reagent made from bromobenzene (110 cubic centimetres) and magnesium (17 grams), stirred and cooled in a bath kept at 0° C. After stirring in the cold for 1 hour, the reaction mixture is heated under reflux for 3 hours and is then cooled to 0° C. and stirred into crushed ice. Concentrated hydrochloric acid is then gradually added to the stirred mixture, cooled to 0° C., until acid to congo red. After standing for 1 hour at 0° C. the salt which separates is filtered off and washed with ether. The salt is suspended in chloroform and the suspension shaken with excess of concentrated ammonia solution and the chloroform layer separated, washed with water and dried. The chloroform is evaporated, leaving 3-N-piperidino-1:1-diphenylpropan-1-ol as a solid residue, which after recrystallisation from benzene or light petroleum, forms crystals which melt at 120—121° C.

3 - N - Piperidino - 1:1 - diphenylpropan-1-ol (1 gram) is dissolved in anhydrous acetone (10 cubic centimetres), methyl iodide (1 gram) added and the mixture boiled under reflux for 15 minutes. On cooling N - methyl - 3-hydroxy-3:3-diphenyl - propylpiperidinium iodide crystallises out and after recrystallisation from alcohol has melting point 214—215° C.

EXAMPLE 2.

A solution of 3 - piperidino - 1 : 1-diphenylpropan-1-ol (3 grams) (prepared as described in Example 1) in concentrated aqueous hydrochloric acid (6 cubic centimetres) and glacial acetic acid (20 cubic centimetres) is boiled under reflux for 30 minutes. The solution is then evaporated to dryness under reduced pressure and the residual solid is dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ethereal solution is dried, the ether evaporated and the residual oil distilled under reduced pressure, when the product, 3-N-piperidino-1 : 1-diphenylprop-1-ene, is collected as a colourless liquid, boiling point 138° C./at 0.1 mm. pressure.

3 - N-Piperidino-1 : 1-diphenylprop-1-ene (1 gram) is dissolved in anhydrous acetone (3 cubic centimetres) and a solution of methyl iodide (1 gram) in acetone (1 cubic centimetre) is added, when heat is developed. After standing for several hours, the crystals of N-methyl-3 : 3-diphenylprop - 2 - enylpiperidinium iodide which separate are removed by filtration and recrystallised from ethyl alcohol, melting point 189—190° C., with decomposition.

EXAMPLE 3.

3 - N - Piperidino-1 : 1-diphenylprop-1-ene is converted to the hydrochloride by passing dry hydrogen chloride into a chloroform solution until acid to congo red and adding ether until crystallisation commences. The hydrochloride is then removed by filtration and recrystallised from a mixture of chloroform and acetone, melting point 209—210° C.

3-N-Piperidino - 1 : 1 - diphenylprop-1-ene hydrochloride (1 gram) in ethyl alcohol (10 cubic centimetres) is shaken at room temperature with platinum oxide (0.02 grams) (prepared according to the directions given in Organic Syntheses, 1932, Collective Vol. 1, *p. 452*) in an atmosphere of hydrogen. When the theoretical amount of hydrogen has been absorbed (after approximately 3 hours), the catalyst is removed by filtration and the alcohol is removed by evaporation under reduced pressure. The residue is recrystallised from a mixture of alcohol and acetone when 3-N-piperidino-1 : 1-diphenylpropane hydrochloride is obtained as crystals, melting point 215—217° C. The free base is obtained by suspending the hydrochloride in water, adding excess aqueous ammonia and extracting with ether. The ethereal extract, after drying and evaporation of ether, yields crystals of 3-N-piperidino-1 : 1-diphenylpropane, melting point 40—41° C.

3 - N - Piperidino - 1 : 1 - diphenylpropane (1 gram) is dissolved in anhydrous acetone (2 cubic centimetres) and methyl iodide (1 gram) in anhydrous acetone (1 cubic centimetre) is added. After standing for 2 hours the crystals of N-methyl-3 : 3-diphenylpropylpiperidinium iodide are filtered off and recrystallised from ethyl alcohol; melting point 175—176° C., with decomposition.

EXAMPLE 4.

3-Dimethylamino - 1 : 1 - diphenylpropan-1-ol is prepared from the ethyl ester of β-dimethylaminopropionic acid (29 grams) and the Grignard reagent made from bromobenzene (110 grams) and magnesium (17 grams) by a method essentially similar to that described in Example 1 (above) for the preparation of 3-N - piperidino-1 : 1-diphenylpropan-1-ol 3 - Dimethylamino-1 : 1-diphenylpropan-1-ol has melting point 166° C. after recrystallisation from benzene or light petroleum.

3-Dimethylamino - 1 : 1 - diphenylpropan-1-ol (4 grams) is dissolved in boiling ethyl alcohol (80 cubic centimetres) and ethyl iodide (5 grams) added and the mixture boiled under reflux for 2 hours. On cooling N-dimethyl-N-ethyl-3-hydroxy-3 : 3 - diphenylpropylammonium iodide crystallises out and melts at 200—201° C., with decomposition, after recrystallisation from ethyl alchohol.

EXAMPLE 5.

N - Dimethyl - N - propyl-3-hydroxy-3 : 3 - diphenylpropylammonium bromide similarly is prepared by boiling 3-dimethylamino - 1 : 1 - diphenylpropan-1-ol with 1-bromo-propane in ethanolic solution for 5 hours (under reflux). The product melts with decomposition at 231—233° C.

EXAMPLE 6.

N - Dimethyl-N-butyl-3-hydroxy-3 : 3-diphenylpropylammonium bromide is prepared from 3 - dimethylamino-1 : 1-diphenylpropan-1-ol and 1-bromobutane in a similar manner to that described in Example 5. It has melting point 233—235° C. (with decomposition).

EXAMPLE 7.

3-Dimethylamino - 1 : 1 - diphenylpropan-1-ol (2 grams) is dissolved in boiling ethyl alcohol (40 cubic centimetres) and benzyl chloride (3 grams) added, and the mixture boiled under reflux for 2 hours. The mixture is cooled, ether (50 cubic centimetres) is gradually added and the crystals of N - dimethyl - N - benzyl-3-hydroxy - 3 : 3 - diphenylpropylammonium chloride filtered off and recrystal-

lised from ethyl alcohol; melting point 251° C., with decomposition.

EXAMPLE 8.

3-Dimethylamino - 1:1 - diphenylpropan-1-ol (6.0 grams) is dissolved in concentrated hydrochloric acid (18 cubic centimetres) and glacial acetic acid (60 cubic centimetres) and the solution boiled under reflux for 20 minutes. The product is then worked up as described in Example 2, when 3-dimethylamino-1:1-diphenylprop-1-ene is obtained as a colourless oil, boiling point 102—3° C./18 mm.

The methiodide (N - trimethyl - 3:3-diphenylprop-2-enylammonium iodide) is prepared by the method described in Example 2. It melts with decomposition at 203—205° C., after recrystallisation from ethanol.

EXAMPLE 9.

3 - Dimethylamino-1:1-diphenylprop-1-ene (5.0 grams) is dissolved in ethanol (20 cubic centimetres), 3% palladised charcoal (1.5 grams) added and the mixture shaken in an atmosphere of hydrogen until no further absorption occurs. The catalyst is filtered off, the alcohol removed from the filtration by evaporation, and the residual oil fractionally distilled under reduced pressure. 3-Dimethylamino - 1:1 - diphenylpropane distils at 183—185° C./16 mm., and crystallises on standing, melting point 44—45° C. (recrystallised from light petroleum).

3-Dimethylamino - 1:1 - diphenylpropane (1.0 gram) is dissolved in acetone (3 cubic centimetres) and methyl iodide (1.0 gram) added. Heat is developed and crystals of N-trimethyl 2:3-diphenylpropylammonium iodide separate. The crystals are filtered off and recrystallised from a mixture of methanol and ethyl acetate; melting point 179—180° C.

EXAMPLE 10.

3 - Diethylamino-1:1-diphenylpropan-1-ol is prepared from the ethyl ester of β-diethylaminopropionic acid (35 grams) and the Grignard reagent made from bromobenzene (110 grams) and magnesium (17 grams) by a method essentially similar to that described in Example 1 (above) for the preparation of 3-N-piperidino - 1:1 - diphenylpropan - 1 - ol. 3-Diethylamino - 1:1 - diphenylpropan-1-ol, purified by distillation under reduced pressure (boiling point 154° C/0.2 mm.) or by recrystallisation from light petroleum, has melting point 53.5° C.

3 - Diethylamino-1:1-diphenylpropan-1-ol (1 gram) is dissolved in anhydrous acetone (2 cubic centimetres), methyl iodide (1 gram) in anhydrous acetone (2 cubic centimetres) added, and the mixture allowed to stand for 2 hours. N-Methyl-N-diethyl - 3 - hydroxy - 3:3-diphenylpropylammonium iodide, which crystallises out, is recrystallised from methyl alcohol and has melting point 198—199° C.

EXAMPLE 11.

3 - Diethylamino-1:1-diphenylpropan-1-ol hydrochloride is dehydrated by the method described in Example 2. 3-Diethylamino-1:1-diphenylprop-1-ene is obtained as a colourless oil, becoming pale yellow on standing, boiling point 110° C./0.05 mm. The hydrochloride prepared therefrom has melting point 146—147° C. (recrystallised from anhydrous acetone).

The tertiary amine (3.0 grams) is dissolved in acetone (5.0 cubic centimetres) and methyl iodide (3.0 grams) in acetone (2 cubic centimetres) gradually added with cooling. The crystalline precipitate of N-methyl-N-diethyl - 3:3 - diphenylprop-2-enylammonium iodide is removed and recrystallised from methanol. It has a melting point of 185—186° C.

EXAMPLE 12.

3-Diethylamino - 1:1 - diphenylprop-1-ene hydrochloride (6.0 grams) in ethanol (15 cubic centimetres) to which 3% palladised charcoal (2.0 grams) is added is shaken in an atmosphere of hydrogen until the calculated volume is absorbed (after approximately 1 hour). After removal of the catalyst by filtration, ether is added to the filtrate until crystallisation of the 3-diethylamino-1:1-diphenylpropane hydrochloride commences. The salt has melting point 145.5° C. and may be recrystallised from acetone. The free base (obtained as a colourless liquid) is converted to the quaternary methiodide (N - methyl - N-diethyl - 3:3 - diphenylpropylammonium iodide) of melting point 162—163° C. (recrystallised from aqueous ethanol) by the method described in Example 2.

EXAMPLE 13.

Ethyl β - di-*n*-propylaminopropionate (prepared as described by Weisel, Taylor, Mosher and Whitmore, *Journal of the American Chemical Society*, 1945, Volume 67, page 1071) (40.2 grams) in anhydrous ether (50 cubic centimetres) treated with the Grignard reagent made from bromobenzene ((110 grams) and magnesium (17 grams) under the conditions described in Example 1, yields 3-di-*n*-propylamino - 1:1 - diphenylpropan-1-ol which is purified by fractional distillation under reduced pressure (boiling point 153—154° C. at 0.1 mm.) and by recrystallisation from light petroleum; the base has melting point 52.5—53.5° C.

The methiodide (N-methyl-N-dipropyl-3:3-diphenyl - 3 - hydroxypropylammo-

nium iodide) prepared therefrom by the method described in Example 2 has melting point 181—183° C., after recrystallisation from aqueous ethanol.

EXAMPLE 14.

Ethyl β-N-phenyl-N-methylaminopropionate (41.4 grams) in ether (100 cubic centimetres), treated with the Grignard reagent prepared from bromobenzene (110 grams) and magnesium (17 grams) in ether (200 cubic centimetres) in a similar manner to that described in Example 1, yields 3-N-phenyl-N methylamino-1:1-diphenylpropan-1-ol, melting point 97° C. (recrystallised from ethanol). The ethyl β-N-phenyl - N - methylaminopropionate used as starting material is prepared by a method essentially similar to that described by Elderfield, Gensler, Bembry, Kremer, Brody, Hageman and Head, *Journal of the American Chemical Society*, 1946, Volume *68*, page 1259, for the preparation of β-arylaminopropionic esters.

A mixture of ethyl acrylate (40g.), methylaniline (42.8 grams) and acetic acid (10 grams) is boiled under reflux for 12 hours, cooled, and taken up in an equal volume of ether. The ethereal solution is then washed with water, then with aqueous sodium bicarbonate solution and finally with water. The ethereal solution is then dried with anhydrous sodium sulphate, the ether evaporated, and the residual oil fractionally distilled under reduced pressure. The required ester is collected at 98—100° C/0.05 mm.

3-N-Phenyl - N - methylamino - 1:1-diphenylpropan-1-ol (2.0 grams) is dissolved in ethanol (5.0 c.c.), methyl iodide (2.0 grams) added and the mixture allowed to stand for 24 hours. The N-dimethyl-N-phenyl - 3:3 - diphenyl-3-hydroxypropylammonium iodide which separates melts with decomposition at 176° C., after recrystallisation from aqueous ethanol.

EXAMPLE 15.

Ethyl - β - N - methyl-N-β-phenylisopropylaminopropionate (49.8 grams) in ether (100 cubic centimetres) is added dropwise to an ethereal solution of the Grignard reagent prepared from bromobenzene (110 grams) and magnesium (17 grams) and the mixture boiled under reflux for 2 hours. The cooled mixture is then poured on to crushed ice (100 grams) and acidified to congo red by the gradual addition of hydrochloric acid (concentrated). A gum, which rapidly solidifies, is precipitated, separated by filtration and washed with ether. The solid is then suspended in water (100 cubic centimetres) and chloroform (100 cubic centimetres) excess aqueous ammonia added with shaking, and the chloroform layer separated and dried over anhydrous sodium sulphate. Dry hydrogen chloride is then passed into the filtered chloroform solution until acid to congo red and other added to the point of crystallisation. 3-N-Methyl-N-2¹-phenyl-1¹-methylethylamino - 1:1 - diphenylpropan-1-ol hydrochloride separates and has melting point 207—208° C. after recrystallisation from aqueous ethanol; the base, liberated from the hydrochloride by addition of aqueous alkali, is a viscous oil.

The ethyl-β-N-methyl-N-β-phenyl*iso*propylminopropionate used as starting material is prepared by allowing a mixture of ethyl acrylate (40 grams) and β-phenylisopropylaminopropionate used as starting material is prepared by allowing a mixture of ethyl acrylate (40 grams) and β-phenyl*iso*propylmethylamine (60 grams) to stand for 48 hours, then boiling under reflux for 4 hours and subsequently fractionally distilling the product under reduced pressure (boiling point 165—166° C./12 mm.).

The methiodide of the base is prepared by mixing with methyl iodide in acetone solution as described in Example 2. The product melts with decomposition at 226° C.

EXAMPLE 16.

Ethyl β-N-pyrolidinopropionate when treated with the Grignard reagent prepared from bromobenzene by the same method as that described in Example 1 yields 3-N-pyrrolidino-1:1-diphenyl-propan-1-ol melting point 171—172° C. (recrystallised from ethyl acetate).

The ethyl β-N-pyrrolidinopropionate is prepared by mixing pyrrolidine (21 grams) with ethyl acrylate (30 grams) and allowing to stand at room temperature for several days. The product is distilled under reduced pressure, the required ester being collected at 108—110° C./23 mm.

3 - N - Pyrrolidino-1:1-diphenylpropan-1-ol (2.0 grams) is dissolved in chloroform (25 cubic centimetres), methyl iodide (2.0 grams) added, and the mixture allowed to stand for 24 hours. The crystals of N-methyl-3:3-diphenyl-3-hydroxypropylpyrrolidinium iodide which separate are recrystallised from methanol; melting point 210° C.

EXAMPLE 17.

Ethyl β-N-morpholinopropionate (prepared as described by Weisel, Taylor, Mosher and Whitmore, *Journal of the American Chemical Society*, 1945, Volume *67*, page 1071,) when treated with the Grignard reagent prepared from bromobenzene by the same method as that described in Example 1 yields 3-N-

morpholino-1:1-dihpenylpropan - 1 - ol melting point 106° C. (recrystallised from light petroleum).

The corresponding methiodide is prepared by the method described in Example 1; it melts with decomposition at 203—204° C.

EXAMPLE 18.

3 - Diallylamino-1:1-diphenylpropan-1-ol is prepared from ethyl β-diallylaminopropionate (39 grams) and the Grignard reagent made from bromobenzene (110 grams) and magnesium (17 grams) by a method essentially similar to that described in Example 1 for the preparation of 3-N-piperidino-1:1-diphenyl-propan-1-ol. The product has boiling point 157—159° C./0.4 mm. after recrystallisation from light petroleum.

3 - Diallylamino-1:1-diphenylpropan-1-ol (3 grams) is dissolved in anhydrous acetone (5 cubic centimetres) and methiodide (2 grams) added to the solution. The fine needles of N-methyl-N-diallyl-3:3 - diphenyl-3-hydroxypropyl - ammonium iodide which quickly separate are recrystallised from aqueous methyl alcohol; melting point 196—197° C., with decomposition.

EXAMPLE 19.

3 - Diallylamino-1:1-diphenylprop-1-ene is prepared from 3-diallylamino-1:1-diphenylpropan-1-ol by dehydration by a method essentially similar to that described in Example 2 for the preparation of 3-piperidino-1:1-diphenyl-prop-1-ene. The product is a colourless oil, of boiling point 134° C./0.2 mm.

3 - Diallylamino-1:1-diphenylprop-1-ene (2 grams) is dissolved in anhydrous acetone (3 cubic centimetres), methyl iodide (2 grams) added and the mixture heated under reflux for 1 hour. After cooling and standing for 24 hours, the crystals of N-methyl-N-diallyl-3:3-diphenylprop-2-enylammonium iodide are separated by filtration and recrystallised from ethanol, melting point 149—151° C. with decomposition.

EXAMPLE 20.

Ethyl β-dimethylaminobutyrate (prepared as described by Breckpot, Bulletin Societe Chimique de Belgique 1923, volume *32*, page 412) when treated with the Grignard reagent prepared from bromobenzene by the same method as that described in Example 1 yields 3-dimethylamino - 1:1-diphenyl-butan-1-ol melting point 125—126° C. (recrystallised from aqueous ethanol). The tertiary amine (2.0 grams) is dissolved in warm acetone (10 cubic centimetres), methyl iodide (2.0 grams) added and the mixture boiled under reflux for 15 minutes. On cooling and standing, the corresponding morpholino-1:1-diphenylpropan - 1 - ol ing point 251° C. after recrystallisation from aqueous ethanol.

EXAMPLE 21.

Dehydration of 3-dimethylamino-1:1-diphenylbutan-1-ol hydrochloride in a similar manner to that described in Example 2 yields 3-dimethylamino-1:1-diphenylbut-1-ene, boiling point 194—196° C./19 mm., (hydrochloride, melting point 160—161° C.)

The methiodide prepared therefrom by the method described in Example 2 melts with decomposition at 210—212° C: after recrystallisation from aqueous ethanol.

EXAMPLE 22.

Hydrogenation of 3-dimethylamino-1:1-diphenylbut-1-ene hydrochloride (4.0 grams) is effected by shaking in ethanol (20 cubic centimetres) with 3% palladised charcoal (2.0 grams) in an atmosphere of hydrogen. When hydrogen absorption has ceased, the catalyst is removed by filtration and the filtrate evaporated to dryness. The residue is dissolved in water, basified with aqueous ammonia and the oil separated by chloroform. After drying and evaporating the chloroform, the product, 3-dimethylamino-1:1-diphenylbutane is distilled under reduced pressure, when it is obtained as a colourless oil, boiling point 176° C./12 mm.

The methiodide prepared therefrom by the method described in Example 2 has melting point 204—205° C. after recrystallisation from ethanol.

EXAMPLE 23.

Ethyl β - diethylaminopropionate (26 grams) in anhydrous ether (50 c.c.) is added dropwise to an ether solution of the Grignard reagent made from *p*-bromotoluene (90 grams) and magnesium (12.8 grams), stirred and cooled in a bath kept at 0° C. After stirring in the cold for 1 hour and boiling under reflux for 2 hours, the reaction mixture is worked up as described in Example 1. The 3-diethylamino-1:1-di - *p* - tolylpropan - 1 - ol so obtained is purified by fractional distillation under reduced presure (boiling point 160—162° C./0.5 mm.) and may be recrystallised from a small volume of light petroleum, melting point 56—58° C.

The methiodide prepared therefrom (method described in Example 2) has melting point 188—189° C. (may be recrystallised from aqueous ethanol).

EXAMPLE 24.

3 - Diethylamino-1:1-di-*p*-tolylpropan-1-ol hydrochloride is dehydrated by the method described in Example 2, when 3-diethylamino-1:1-di-*p*-tolylprop-1-ene is obtained as a colourless liquid, boiling point 146—150° C./0.3 mm. pressure.

The tertiary base (1.5 grams) in methanol (3 cubic centimetres) is mixed with methyl iodide (1.5 grams) when heat is developed. After standing for several hours, anhydrous ether is added dropwise with stirring until precipitation of the methiodide is complete. N-Methyl-N-diethyl-3:3-di-*p*-tolylprop-2-enyl-ammonium iodide melts with decomposition at 141—143° C. after recrystallisation from a mixture of ethyl acetate and ethanol.

EXAMPLE 25.

3-Diethylamino-1:1-di-*p*-tolylprop-1-ene hydrochloride (melting point 179—180° C.; which was obtained from the base described in Example 24) when hydrogenated by the method described in Example 3, yields 3-diethylamino-1:1-di-*p*-tolylpropane hydrochloride, melting point 136—138° C. (recrystallised from methyl acetate) from which the base is obtained as an oil.

The methiodide prepared from the tertiary amine, as described in Example 2, has melting point 169—170° C. after recrystallisation from ethanol.

EXAMPLE 26.

β-Diethylaminopropiophenone hydrochloride (prepared as described by Blicke and Burckhalter, *Journal of the American Chemical Society*, 1942, Volume *64*, page 451) (48.3 grams) is added in small portions to the Grignard reagent prepared from benzyl chloride (76 grams) and magnesium (14.6 grams) in ether (100 cubic centimetres), stirred and cooled to 0° C. The reaction and working up of the product is then carried out as described in Example 1. 4-Diethylamino-1:2-diphenylbutan-2-ol is obtained as crystals, melting point 54—55° C. (recrystallised from light petroleum).

The methiodide prepared therefrom by the method described in Example 2, has melting point 197—198° C. after recrystallisation from methanol.

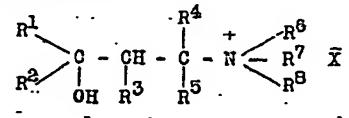
EXAMPLE 27.

β-Diethylaminopropionphenone hydrochloride (48.3 grams) is added in small portions to the Grignard reagent prepared from *cyclo*hexyl bromide (98 grams) and magnesium (14.6 grams) in 100 c.c ether stirred and cooled to 0° C. After boiling under reflux for 12 hours the product is worked up by a similar method to that described in Example 1. 3-Diethylamino-1-*cyclo*hexyl-1-phenylpropan-1-ol is purified by distillation under reduced pressure (boiling point 132—135° C./0.02 mm.) and by recrystallisation from light petroleum (melting point 50.5—52° C.).

The tertiary base (1.0 gram) is dissolved in acetone (3 cubic centimetres) and methyl iodide (1.0 gram) added. After standing for several hours, crystallisation of the product is completed by gradual addition of anhydrous ether N-Methyl-N-diethyl-3-*cyclo*hexyl-3-phenyl-3-hydroxypropylammonium iodide has melting point 160—162° C. after recrystallisation from ethyl acetate and ethanol.

Having now particularly described and ascertained the nature of our said invention, and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the preparation of N-trisubstituted-$\gamma\gamma$-disubstituted-γ-hydroxypropylammonium salts, N-trisubstituted-$\gamma\gamma$-disubstituted-allylammonium salts and N-trisubstituted-$\gamma\gamma$-disubstituted-propylammonium salts of the general formula:—



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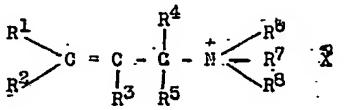

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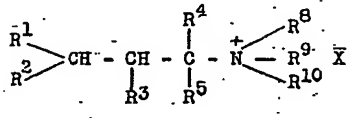


(III)

wherein R^1 and R^2 may be either identical or different and denote aryl, aralkyl or *cyclo*alkyl radicals, optionally substituted, for example, by alkyl or alkoxy groups,

R^3 denotes hydrogen or an alkyl radical,

R^4 denotes hydrogen or an alkyl radical,

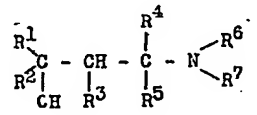
R^5 denotes hydrogen or an alkyl, aryl or aralkyl radical.

R^6 and R^7 may be either identical or different and denote alkyl, alkenyl, *cyclo*alkyl, aryl or aralkyl groups, or $—NR^6R^7$ may denote the pyrrolidino-, morpholino, or piperidino-group, optionally substituted by one or more alkyl groups,

R^8 denotes an alkyl or aralkyl radical,

R^9 and R^{10} may be either identical or different and denote alkyl, *cyclo*alkyl, aryl or aralykyl radicals, or $—NR^9R^{10}$ may denote the pyrrolidino-, morpho-

lino-, or piperidino-group, optionally substituted by one or more alkyl groups, and $\overline{X}$ is an acid radical such as chloride, bromide, iodide or methosulphate radical, comprising treating an alkyl or aralkyl halide or other reactive acid salt R^8X with a tertiary amine of the general formula



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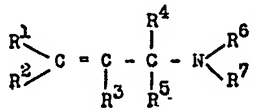

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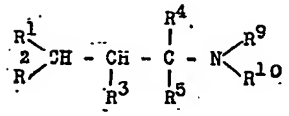

(VI)

(wherein R^1, R^2, R^3, R^4, R^5, R^6 R^7, R^9 and R^{10} have the same meaning as above) or *vice versa*.

2. The process claimed in claim 1 in which an excess of the reactive acid salt R^8X is present during the reaction.

3. The process claimed in claim 1 in which a solvent for both reactants is present during the reaction and the reaction is carried out at room temperature or at the boiling point of the solvent or at some intermediate temperature.

4. The process claimed in claim 3 in which the solvent is so selected and is present in such quantity that the desired quaternary salt crystallizes from the reaction mixture on cooling the latter.

5. The process claimed in claim 3 in which a liquid in which the reaction product is insoluble is added gradually to the reaction mixture after the reaction has been completed, until crystallization of the reaction product occurs.

6. The process claimed in claim 3 in which the solvent employed is anhydrous acetone, ethyl alcohol or dioxan.

7. A process for preparing compounds having the general formulae I, II or III given in claim 1, substantially as hereinbefore described.

8. A process for preparing a chemical compound having a formula within the scope of the general formulae I, II or III given in claim 1, substantially as described in any one of the Examples hereinbefore given.

9. A chemical compound when prepared by the process claimed in any preceding claim.

Dated this 7th day of May, 1948.

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